REMARKS

Reconsideration of the present application in view of the above amendments and following remarks is requested respectfully.

Status of the Claims

Claims 100, 102, 103, 127, 194 to 200, 203, 210 to 228, 294 to 300, 303, 310 to 329, 331 to 337, and 347 to 356 are pending in the application. No claims have been added or canceled. Claims 100 and 127 have been amended.

Claims 100 and 127, the only two pending independent claims, have been amended to more clearly define what Applicants consider to be their invention. The amendments are fully supported by the specification, and therefore do not constitute new matter. Gas-filled vesicles as defined in Applicants' claims are described in the application as filed, for example, at page 12, line 19, to page 13, line 9, and page 14, lines 1 to 16. The use of crosslinked proteins and polymers to stabilize microbubbles is described on page 17, line 21, to page 18, line 28.

Applicants thank the Examiner for taking the time to discuss this application, and the previously pending rejections in the interview held prior to issuance of the latest Office Action. Applicants further acknowledge and thank the Examiner for the withdrawal of all previously pending rejections.

Applicants have filed formal drawings, concurrent with the instant Amendment, under separate cover.

Summary of the Invention

The invention defined by the amended claims is directed to formulations for diagnostic or therapeutic use that comprise targeted gas-filled vesicles. As amended herein, the

vesicles comprise one or more membranes *encapsulating an internal void that contains a gas selected from the group consisting of perfluorocarbons and sulfur hexafluoride*, and methods for therapeutic delivery *in vivo* that comprise administering such formulations. The membrane comprises a phospholipid, as well as a conjugate that comprises a lipid, a linking group, and a targeting ligand. As amended herein, the membrane is *substantially free of crosslinked proteins and polymers.*

Response to Rejection

All pending claims stand rejected under 35 U.S.C. § 103 over either Schneider, et al, U.S. Patent No. 5,643,553 ("Schneider"), or Grinstaff, et al., U.S. Patent No. 5,498,421 ("Grinstaff"), in view of Wallach, et al, U.S. Patent No. 4,853,228 ("Wallach"), Allen, et al, U.S. Patent No. 5,620,689 ("Allen"), and Ginsberg, U.S. Patent No. 5,656,442 ("Ginsberg"). As the discussion to follow makes clear, these references, in any proper combination, fail to render Applicants' invention obvious.

Schneider, in view of Wallach, Allen and Ginsberg

Schneider is directed to microbubble suspensions in aqueous phases, said to be usable as ultrasound contrast agents. *See* abstract. Schneider makes very clear, however, that the microbubbles described in that patent art NOT the membrane bounded structures of the present invention. Specifically, Schneider contrasts the microbubbles described therein from what it calls "microballoons," *i.e.*, "gas bodies with a material boundary or envelope formed of molecules other than that of the liquid of suspension." *See* Schneider, col. 1, lines 38 to 42. Schneider goes on to clarify that the microbubbles described therein are also not gas-filled liposomes, as described, for example, in Ryan, U.S. Patent No. 4,900,540, stating that "gas-filled liposomes . . . belong to the class of microballoons and not to that of the microbubbles of the present invention."

It is thus eminently clear that Schneider *teaches away* from the use of gas bubbles which are *encapsulated within one or more membranes*, as recited in Applicants' claims. Applicants respectfully submit, therefore, that regardless of whether Schneider may suggest targeting its microbubbles, and regardless of whether the secondary references cited in the Office Action may suggest the use of a conjugate as defined by Applicants' claims to achieve targeting, *Schneider's microbubbles are still different than Applicants' vesicles*. The references also fail to suggest how Schneider's microbubbles could be modified to include such a conjugate in the encapsulating membrane, *because Schneider's microbubbles have no such membrane*. Accordingly, the combination of references set forth in the Office Action fails to establish the *prima facie* obviousness of Applicants' claims.

Grinstaff in view of Wallach, Allen and Ginsberg

Grinstaff is directed to compositions in which a biologic is associated with a polymeric shell formulated from a biocompatible material. *See* abstract. Although Grinstaff may teach that the polymeric shell may optionally be modified to include a phospholipid, such as phosphatidylcholine or phosphatidylethanolamine, *see* col. 12, lines 20 to 27, Grinstaff makes crystal clear that the microparticles described therein are made with a polymeric shell that is made from a biocompatible material that is crosslinked by disulfide bonds. *See* col. 6, lines 14 to 15. Grinstaff does not describe any entities whatsoever that are *substantially free of crosslinked proteins and polymers*, as recited Applicants' claims, as amended herein.

Thus, as discussed above with regard to Schneider, regardless of whether the secondary references cited in the Office Action may suggest the use of a conjugate as defined by Applicants' claims to achieve such ends, *Grinstaff's polymeric microparticles are different than Applicants' vesicles*. And, as discussed above with regard to Grinstaff, the combined references fail to teach how a conjugate, such as recited in Applicants' claims, could be introduced into

Grinstaff's polymeric shell. Moreover, even if such modification were made, the resulting microparticle would STILL be different from those instantly claimed, because such vesicles would not be substantially free of crosslinked proteins and polymers. Accordingly, the combination of references fail to establish the *prima facie* obviousness of Applicants' claims.

Applicants respectfully insist, therefore, that even without getting into the issue of whether the references teach other elements of Applicants' claims, such as the use of SF_6 or a perfluorocarbon gas (which they do not), or whether the combination of selected elements made in the Office Action is proper, or could have reasonably been expected to succeed as of the application's effective filing date (which Applicants submit is not the case), it is eminently clear from the foregoing that Applicants' claims define over the combination of Allen, Wallach and Ginsberg with either Schneider or Grinstaff. Applicants respectfully request, therefore, that the rejection under Section 103 be withdrawn, and that the patentability of Applicants' claims be recognized.

CONCLUSION

Applicants believe that the foregoing constitutes a full and complete response to the Office Action of record. Accordingly, an early and favorable allowance of all of pending Claims 100, 102, 103, 127, 194 to 200, 203, 210 to 228, 294 to 300, 303, 310 to 329, 331 to 337, and 347 to 356 is requested respectfully.

In the event that the Examiner is not persuaded that the claims as amended herein are allowable, Applicants respectfully request that the Examiner contact Applicants' undersigned representative to arrange for an interview to discuss the application further.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**" Also attached is a copy of the claims Applicants believe to be pending after entry of the amendment, as requested by the Examiner.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 113, 115, 122, 124, 229 to 238, 245 to 248, 255 to 270, 277 to 280, 287 to 292, and 357 to 411 have been canceled, without prejudice.

100. (Three times amended) A formulation for therapeutic or diagnostic use comprising targeted [lipid] gas-filled vesicles [having encapsulated therein] which comprise one or more membranes encapsulating an internal void that contains a gas selected from the group consisting of perfluorocarbons and sulfur hexafluoride, [said targeted lipid vesicles comprising] said membrane comprising a phospholipid, and being substantially free of crosslinked proteins and polymers, and further comprising a conjugate that comprises a lipid, a linking group, and a targeting ligand, wherein said linking group is a hydrophilic polymer that is covalently bound to both said lipid and said targeting ligand, and is selected from the group consisting of polyethylene glycol (PEG), polypropylene glycol, polyvinylalcohol, polyvinylpyrrolidone, and copolymers thereof, and wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIbIIIa receptor.

127. (Three times amended) A method for the therapeutic delivery *in vivo* of a bioactive agent comprising administering to a patient a therapeutically effective amount of a formulation which comprises, in combination with a bioactive agent, targeted [lipid] gas-filled vesicles [having encapsulated therein] which comprise one or more membranes encapsulating an internal void that contains a gas selected from the group consisting of perfluorocarbons and

sulfur hexafluoride, [said targeted lipid vesicles comprising] said membrane comprising a phospholipid, and being substantially free of crosslinked proteins and polymers, and further comprising a conjugate that comprises a lipid, a linking group, and a targeting ligand, wherein said linking group is a hydrophilic polymer that is covalently bound to said lipid and said targeting ligand, and is selected from the group consisting of polyethylene glycol (PEG), polypropylene glycol, polyvinylalcohol, polyvinylpyrrolidone, and copolymers thereof, and wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIbIIIa receptor.